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Acute Stent Thrombosis After Primary Percutaneous Coronary Intervention

Insights From the EUROMAX Trial (European Ambulance Acute Coronary Syndrome Angiography)

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ABSTRACT

OBJECTIVES This study sought to determine clinical, procedural, and treatment factors associated with acute stent thrombosis (AST) in the EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial.

BACKGROUND Bivalirudin started during transport for primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction significantly reduced major bleeding compared with heparin with or without glycoprotein IIb/IIIa inhibitors (GPI), but it was associated with an increase in AST.

METHODS We compared patients with (n = 12) or without AST (n = 2,184) regarding baseline, clinical, and procedural characteristics and antithrombotic treatment strategies (choice of $P2Y_{12}$ inhibitor, post-primary PCI bivalirudin infusion dose [0.25 mg/kg/h, or BIV-LOW] vs. [1.75 mg/kg/h, or BIV-PCI] vs. heparin ± GPI). Logistic regression was performed to identify independent correlates of AST.

RESULTS The overall AST rate was 0.6% and was higher with bivalirudin than with heparin ± GPI (1.1% vs. 0.2%; p = 0.007). Median time to AST was 2.3 h (interquartile range: 1.9 to 2.8 h). Patients with AST had less hypertension (2 of 14 [14.0%] vs. 961 of 2,182 [44.0%]; p = 0.03), and more frequently received GPI (11 of 14 [78.6%] vs. 880 of 2,183 [40.3%]; p = 0.004). Multivariate analysis using Firth penalized maximum likelihood estimation found hypertension (odds ratio [OR]: 0.24, 95% confidence interval [CI]: 0.07 to 0.92; p = 0.037) and BIV-LOW (OR: 5.8, 95% CI: 1.5 to 22.2; p = 0.010) predictive of AST. Choice of $P2Y_{12}$ inhibitor had no impact on AST. Compared with heparin ± GPI, AST rates were higher for BIV-LOW (11 of 670 [1.6%] vs. 2 of 947 [0.2%]; p = 0.008), but not different for BIV-PCI (1 of 244 [0.4%]; p = 0.588).

CONCLUSIONS In this post-hoc analysis from EUROMAX, AST occurred very early and was not mitigated by the novel $P2Y_{12}$ inhibitors. Prolonging the bivalirudin infusion at the PCI dose (but not at a lower dose) appeared to mitigate the risk of AST. (J Am Coll Cardiol Intv 2015;8:214–20) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Primary percutaneous coronary intervention (pPCI) with stent implantation is recognized as the treatment of choice for most patients with evolving ST-segment elevation myocardial infarction (STEMI). In these patients, an increased risk of early stent thrombosis (ST) has been noted compared with patients with stable disease and a large number of patient-related, lesion-related, procedural, and post-procedural factors have been associated with ST, including type of stent, lesion characteristics, and thrombus burden (1–5). The choice of antithrombotic therapy in pPCI is an additional important determinant of clinical outcomes, including rates of ST. In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, the largest pPCI trial to date, compared with unfractionated heparin and glycoprotein IIb/IIIa inhibitors (GPI), bivalirudin reduced rates of net adverse clinical events, major bleeding, and death at 30 days with a survival benefit that extended to 3 years (6,7). However, an absolute

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1% excess of acute stent thrombosis (AST) was observed in the bivalirudin arm with the difference in ST rates between treatments no longer present at 30 days (1). Since the HORIZONS-AMI trial was conducted, pPCI practice has evolved with increasing rates of prehospital diagnosis and initiation of treatment (8,9), use of radial access for catheterization (10–12), and use of the novel oral $P2Y_{12}$ inhibitors ticagrelor and prasugrel, whereas routine use of GPI has been on the decline (13–17). The EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial was designed to test whether bivalirudin, initiated during transport for pPCI in STEMI patients, was superior to the use of heparin-based anticoagulation in the setting of contemporary practice (18). Consistent with the outcomes in HORIZONS-AMI, EUROMAX demonstrated a significant decrease in the primary endpoint of death and major bleeding with bivalirudin, but also showed the same 1% absolute increase in AST when compared with use of heparin with optional GPI, despite the use of an extended, albeit primarily low dose, bivalirudin infusion for up to 4 h after pPCI (8).

The aims of the present analysis were to determine whether clinical, procedural, or antithrombotic treatment-related factors, such as the choice of dose for the prolonged bivalirudin infusion, were associated with AST in the EUROMAX trial.

METHODS

EUROMAX randomized 2,198 patients transported for pPCI following a presumed diagnosis of STEMI (8). The details of the EUROMAX study design have been previously published (18). In brief, all patients had to be scheduled for angiography with the intention of performing pPCI within 2 h after first medical contact. The main exclusion criteria were treatment with any anticoagulant before randomization, recent surgery, and a history of bleeding. Patients were identified, initial consent was obtained, randomization was performed, and study drug administration was initiated in the ambulance or in a non-PCI-capable hospital. Patients were transported urgently to the pPCI hospital, where treatment was continued and outcomes data collected. All patients initially provided full or abridged written or oral informed consent in the ambulance or non-PCI hospital according to local ethical rules. This consent was subsequently confirmed by a more formal final written informed

ABBREVIATIONS AND ACRONYMS

AST = acute stent thrombosis

BIV-LOW = reduced dose of bivalirudin

BIV-PCI = full dose of bivalirudin

CABG = coronary artery bypass graft

GPI = glycoprotein inhibitor

IDR = ischemia-driven revascularization

OR = odds ratio

PCI = percutaneous coronary intervention

pPCI = primary percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

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consent during hospitalization. The study was approved by both local ethics committees and national health authorities (18).

TREATMENT. The patients were randomized to treatment with either bivalirudin or heparin (unfractionated or low-molecular-weight heparin) with or without a GPI. Patients who were assigned to the bivalirudin group received a bolus of 0.75 mg/kg of body weight, followed by an infusion of bivalirudin of 1.75 mg/kg/h. The protocol specified that the bivalirudin infusion should be continued for 4 h after pPCI at the reduced dose of 0.25 mg/kg/h (BIV-LOW); the option to prolong the infusion at the full PCI dose of 1.75 mg/kg/h (BIV-PCI) for up to 4 h was also allowed. Bailout use of GPI in the bivalirudin arm was allowed in the event of massive thrombus burden or microvascular obstruction (no reflow). Patients who were assigned to the heparin arm (control group) received either unfractionated heparin (100 IU/kg without a GPI or 60 IU/kg with a GPI) or an intravenous bolus of enoxaparin (0.5 mg/kg). The use of GPI was left to the physician's preference and was categorized as either "routine" when started before the index procedure (emergent angiography ± PCI) or "bailout" when started during or after the procedure for the management of large thrombus burden or no reflow. Any GPI could be used at the approved doses and regimens. All patients received aspirin and a loading dose of an approved $P2Y_{12}$ inhibitor as early as possible after first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to the physician's discretion (8).

STATISTICAL ANALYSIS. Baseline, clinical, and procedural characteristics and treatment strategies were compared between patients with or without AST using the chi-square test and the Wilcoxon signed rank nonparametric test. Comparison of outcomes between the treatment arms was done using the chi-square test and the log-rank test. Logistic regression using Firth penalized maximum likelihood estimation was performed to determine independent predictors of AST. The initial list of candidate variables included the following: age >65 years, sex, anemia, renal function, diabetes, hypertension, hyperlipidemia, smoker, previous PCI, myocardial infarction, or coronary artery bypass graft (CABG) surgery; choice of $P2Y_{12}$ inhibition (clopidogrel vs. newer agents); occurrence of procedural complications; pre-PCI TIMI (Thrombolysis In Myocardial Infarction) flow grade (0/1 vs. 2/3); single- or multivessel disease; Killip class II to IV versus class I; access site (femoral vs. radial); drug-eluting stents; and anticoagulant strategy: BIV-LOW versus heparin plus optional GPI or BIV-PCI versus heparin plus optional GPI. From the initial list of 19 variables, only 3 (age >65 years, hypertension, and BIV-LOW) were found to be significant and only hypertension and BIV-LOW were significant in the final model.

STUDY OUTCOMES. The primary endpoint of the EUROMAX trial was a composite of death and non-CABG-related protocol-defined major bleeding at 30 days. The key secondary endpoint was the composite of death, reinfarction, or non-CABG major bleeding. Additional pre-specified secondary endpoints included the following: major adverse cardiac events (death, reinfarction, ischemia-driven revascularization [IDR], or stroke); net adverse clinical events (death, reinfarction, IDR, stroke, or non-CABG major bleeding); each of the components of the primary and secondary composite endpoints; IDR; ST (as defined by the Academic Research Consortium (19)); and a composite of reinfarction, IDR, or ST.

The protocol definition of non-CABG major bleeding has been previously published (18). Bleeding events were also classified using TIMI and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria (20,21).

All deaths, bleeding episodes, reinfarction, IDR, ST, and strokes were adjudicated by a blinded clinical events committee.

The primary outcome for the present analysis was the occurrence of Academic Research Consortium-defined AST (i.e., ST occurring within 24 h after pPCI).

RESULTS

Among 2,218 patients enrolled in the trial, 2,198 provided full informed consent and were included in the intention-to-treat population, which comprised the population for the present analysis. The 2,198 patients were randomized to treatment with either bivalirudin (n = 1,089) or heparin ± GPI (n = 1,109). The overall rate of AST was 0.6% (n = 14) and the baseline characteristics of patients with and without AST is presented in **Table 1**. Patients with AST presented with numerically fewer risk factors despite older age. Patients with AST versus those without AST had less hypertension (14.0% vs. 44.0%; p = 0.03). Procedural characteristics and concomitant antiplatelet therapy from the pre-hospital phase through discharge are shown in **Table 2**. Patients with AST more often had procedural complications (21.4% vs. 6.6%; p = 0.03) and numerically more right coronary artery interventions (64.3% vs. 43.7%; p = 0.12). Patients with AST were also more likely to have received

TABLE 1 Baseline Characteristics

	Acute ST (n = 14)	No Acute ST (n = 2,184)	p Value
Age (yrs) median (IQR)	63 (54, 72)	61 (62, 71)	0.50
Age >65 yrs	6 (42.9)	822 (37.6)	0.69
Female	5 (35.7)	518 (23.7)	0.29
Diabetes	1 (7.1)	295 (13.5)	0.49
Hypertension	2 (14.3)	961 (44.0)	0.03
Hyperlipidemia	3 (21.4)	812 (37.2)	0.22
Current smoker	3 (21.4)	922 (42.3)	0.13
Previous myocardial infarction	0 (0.0)	193 (8.8)	0.24
Previous PCI	0 (0.0)	205 (9.4)	0.22
Previous CABG	0 (0.0)	47 (2.2)	0.58
Killip class II–IV	1 (7.7)	145 (7.3)	0.96
Anemia	0 (0.0)	277 (14.1)	0.14
Creatinine clearance			
≤60 ml/min	0 (0.0)	312 (15.7)	0.27*
>60 ml/min	14 (100.0)	1,673 (84.3)	

Values are n (%). *This p value represents intracategory differences.

CABG = coronary artery bypass graft; IQR = interquartile range; PCI = percutaneous coronary intervention; ST = stent thrombosis.

TABLE 2 Procedural Characteristics and Treatments

	Acute ST (n = 14)	No Acute ST (n = 2,184)	p Value
Single-vessel disease	6 (42.9)	1,141/2,138 (53.4)	0.51
PCI done	14 (100.0)	1,875/2,184 (85.9)	0.13
Left anterior descending artery	5 (35.7)	843/1,875 (45.0)	0.49
Left circumflex coronary artery	0 (0.0)	247/1,875 (13.2)	0.15
Right coronary artery	9 (64.3)	820/1,875 (43.7)	0.12
Balloon angioplasty only	0 (0.0)	90/1,875 (4.8)	0.40
Stent implanted	14 (100.0)	1,719/1,875 (91.7)	0.26
Drug-eluting stent	7 (50.0)	1,060/1,875 (56.5)	0.62
Thrombectomy	5 (35.7)	597/1,875 (31.8)	0.76
Procedural complication	3 (21.4)	123/1,875 (6.6)	0.03
Pre-PCI TIMI flow grade			
0/1	7/13 (53.8)	1,149/1,850 (62.1)	0.72*
2	3/13 (23.1)	298/1,850 (16.1)	
3	3/13 (23.1)	403/1,850 (21.8)	
Post-PCI TIMI flow grade			
0/1	0/13 (0.0)	34/1,849 (1.8)	0.87*
2	0/13 (0.0)	60/1,849 (3.2)	
3	13/13 (100.0)	1,755/1,849 (94.9)	
Aspirin use	14 (100.0)	2,181/2,183 (99.9)	0.91
$P2Y_{12}$ inhibitor loading dose (overall)	13 (100.0)	2,093/2,136 (98.0)	0.61
Clopidogrel	5/13 (38.5)	1,064/2,091 (50.9)	0.05*
Prasugrel	2/13 (15.4)	627/2,091 (30.0)	
Ticagrelor	6/13 (46.2)	400/2,091 (19.1)	
Glycoprotein IIb/IIIa inhibitor use	11/14 (78.6)	880/2,183 (40.3)	0.004
Routine	3/11 (27.3)	688/880 (78.2)	<0.001*
Bailout	8/11 (72.7)	192/880 (21.8)	

Values are n (%) or n/N (%). *These p values represent intracategory differences.

TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

GPI (78.6% vs. 40.3%; p = 0.004). Of note is that in patients with AST in the heparin group (n = 2) GPI administration was routine rather than bailout.

The rate of AST was higher with bivalirudin than with heparin ± GPI (1.1% vs. 0.2%; p = 0.007). Cases of AST were clustered in the first few hours after pPCI with a median time of occurrence of just 2.3 h (interquartile range: 1.9 to 2.8 h) from the start of angiography (Figure 1). None of the AST cases were fatal. Of the 12 patients with AST who received bivalirudin, 11 received BIV-LOW and 1 received BIV-PCI. In the multivariate analysis using Firth penalized maximum likelihood estimation hypertension (odds ratio [OR]: 0.24, p = 0.037) and receipt of BIV-LOW (OR: 5.8, p = 0.010) were predictors of AST. The rate of AST in BIV-LOW was significantly higher than with heparin ± GPI (11 of 670 [1.6%] vs. 2 of 947 [0.2%]; p = 0.008), whereas the AST rate in patients who received BIV-PCI was comparable to that for patients treated with heparin ± GPI. Table 3 provides outcomes according to anticoagulant strategy and post-PCI bivalirudin infusion dose. Of the patients randomized to bivalirudin who underwent pPCI, 73.3% (670 of 914) received the BIV-LOW infusion after the PCI at 0.25 mg/kg/h (median duration 240 min), and 26.7% (244 of 914) continued the infusion at the PCI dose (total median duration of 240 min from the start of PCI). The bleeding risk was not increased among the patients in the BIV-PCI group compared with those in the BIV-LOW group (2.9% vs. 2.4%) and bleeding rates were lower than that observed in the heparin ± GPI treated group (6%). Reasons for continuing with the BIV-PCI dose were not collected. There were differences in clinical characteristics between patients who received BIV-LOW and BIV-PCI for the extended infusion. Among the latter, there were more smokers, more hyperlipidemia, hypertension, and left main disease, fewer patients treated with $P2Y_{12}$ inhibitors before angiography, more bailout GPI use, less thrombectomy, fewer patients with post-PCI TIMI flow, and higher incidence of failed procedures. Overall patient and procedural risk appeared to be higher in the BIV-PCI group, which may in turn have been the determinant for the choice of the higher dose for the prolonged infusion. Accordingly, clinical outcomes in the BIV-PCI group may also have been a reflection of their clinical and procedural profile.

The cumulative incidence of ST events in the first 24 h and in the first 30 days are shown in Figures 1A and 1B, respectively.

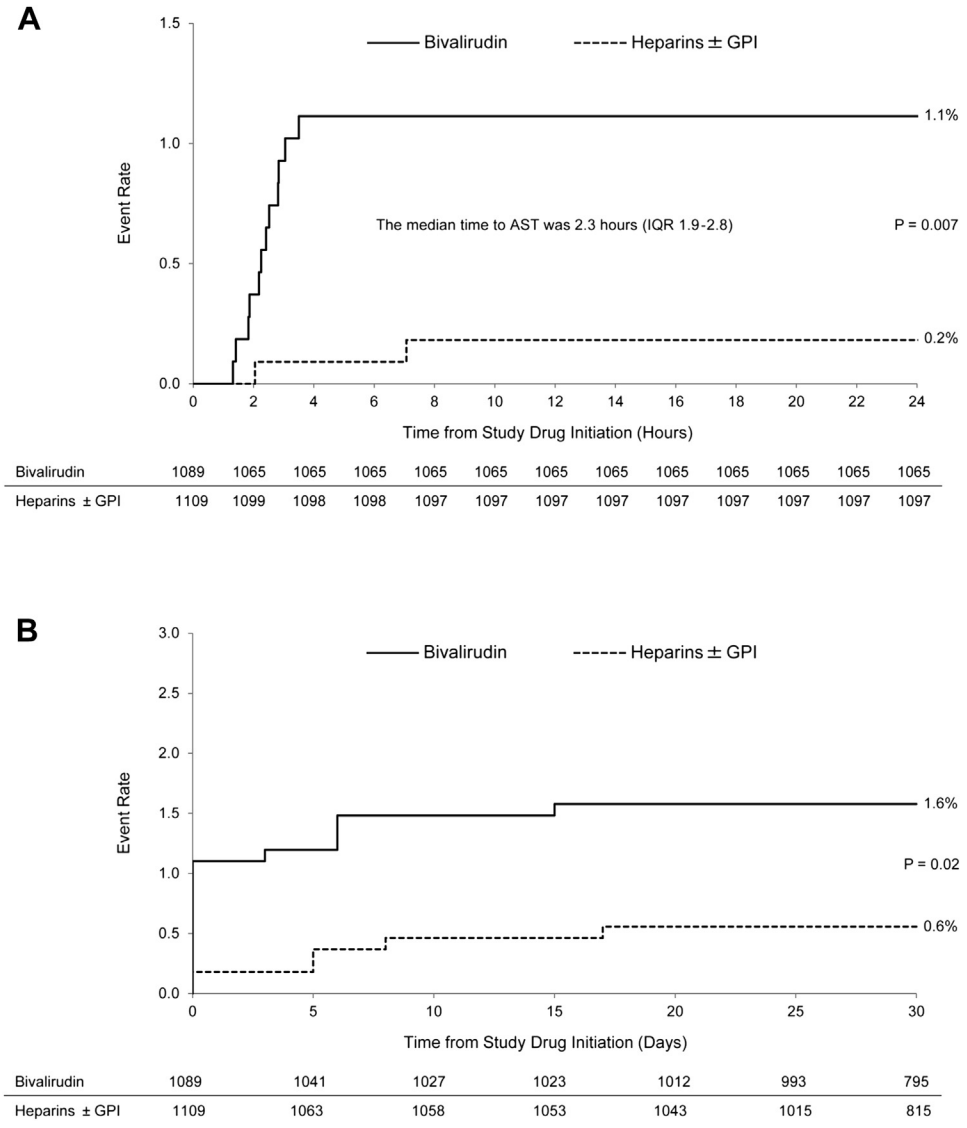

FIGURE 1 Acute Stent Thrombosis

Cumulative incidence rates of first occurrence of stent thrombosis in the first 24 h **(A)** and the first 30 days **(B)** from study drug initiation. AST = acute stent thrombosis; GPI = glycoprotein IIb/IIIa inhibitors; IQR = interquartile range.

The choice of oral $P2Y_{12}$ inhibitor (clopidogrel vs. prasugrel or ticagrelor) did not appear to affect the rates of 30-day ST or AST. Specifically, AST rates among patients receiving prasugrel or ticagrelor was 0.8% (8 of 1,035) versus 0.5% (5 of 1,069) in patients receiving clopidogrel. The overall 30-day rate of definite ST was 1.1% (13 of 1,135) among patients receiving the new oral $P2Y_{12}$ inhibitors and 1.0% (8 of 784) in patients receiving clopidogrel.

DISCUSSION

In the EUROMAX trial, the overall incidence of AST was low (0.6%), but the risk was higher among patients randomized to bivalirudin. This is in keeping with similar observations from HORIZONS-AMI. Although the absolute number of AST cases was small, thereby precluding the definitive assessment of associated factors, EUROMAX provided additional information on AST in the setting of contemporary

TABLE 3 Comparison of Outcomes by Randomized Treatment Group and Bivalirudin Post-PCI Infusion Dose*

	Heparin ± GPI (n = 947)	Bivalirudin Prolonged at Low Dose (n = 670)	RR (95% CI)†	p Value†	Bivalirudin Prolonged at PCI Dose (n = 244)	RR (95% CI)‡	p Value‡
Primary outcome—death or non-CABG major bleeding	76 (8.0)	22 (3.3)	0.41 (0.26-0.65)	0.0002	18 (7.4)	0.92 (0.56-1.51)	0.738
Key secondary outcome—death, reinfarction, or non-CABG major bleed	84 (8.9)	36 (5.4)	0.61 (0.42-0.88)	0.009	20 (8.2)	0.92 (0.58-1.47)	0.740
All-cause death	25 (2.6)	9 (1.3)	0.51 (0.24-1.08)	0.080	11 (4.5)	1.71 (0.85-3.42)	0.131
Ischemia-driven revascularization	17 (1.8)	18 (2.7)	1.50 (0.78-2.88)	0.228	3 (1.2)	0.68 (0.20-2.32)	0.543
Reinfarction—MI	9 (1.0)	16 (2.4)	2.51 (1.12-5.65)	0.026	2 (0.8)	0.86 (0.19-3.97)	0.849
Definite ST	6 (0.6)	15 (2.2)	3.53 (1.38-9.06)	0.009	1 (0.4)	0.65 (0.08-5.35)	0.686
Acute, ≤24 h	2 (0.2)	11 (1.6)	7.77 (1.73-34.96)	0.008	1 (0.4)	1.94 (0.18-21.31)	0.588
Subacute, >24 h to 30 days	4 (0.4)	4 (0.6)	1.41 (0.35-5.63)	0.620	0 (0.0)	N/A	N/A
Protocol major bleeding	57 (6.0)	16 (2.4)	0.40 (0.23-0.68)	0.0009	7 (2.9)	0.48 (0.22-1.03)	0.060
Protocol minor bleeding	74 (7.8)	36 (5.4)	0.69 (0.47-1.01)	0.057	11 (4.5)	0.58 (0.31-1.07)	0.081
MACE—death, MI, IDR, or stroke	48 (5.1)	32 (4.8)	0.94 (0.61-1.46)	0.789	17 (7.0)	1.37 (0.81-2.35)	0.244
NACE—death, MI, IDR, stroke, or non-CABG major bleeding	97 (10.2)	43 (6.4)	0.63 (0.44-0.88)	0.008	23 (9.4)	0.92 (0.60-1.42)	0.706

Values are n (%) unless otherwise specified. *Data are not available regarding a post-PCI infusion for 35 patients. †The RR and p values are for the comparison of heparin with optional GPI versus bivalirudin with prolonged low-dose infusion. ‡The RR and p values are for comparison of heparin with optional GPI versus bivalirudin with prolonged PCI dose infusion.

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; IDR = ischemia-driven revascularization; MACE = major adverse cardiac events; MI = myocardial infarction; N/A = not applicable; NACE = net adverse clinical events; RR = relative risk; other abbreviations as in Table 1.

pPCI. Importantly, EUROMAX confirmed that the risk period for AST appears to be limited to the first few hours after pPCI despite the fact that the Academic Research Consortium definition encompasses the first 24 h.

There were 2 distinct treatment strategies incorporated in the EUROMAX trial that had the potential to mitigate the risk of excess AST, namely, the extended infusion of bivalirudin and the use of the newer $P2Y_{12}$ inhibitors. According to the results of this analysis, neither the use of prasugrel or ticagrelor, nor a prolonged low-dose bivalirudin infusion were able to reduce the AST risk. However, this post-hoc analysis suggests that the selection of the full PCI dose for the prolonged post-procedural infusion may be associated with an AST risk that is comparable to that observed with heparin ± GPI. The higher infusion dose did not seem to increase the risk for bleeding, because major bleeding rates did not appear to be substantially different between the 2 infusion doses. As stated previously, both the choice for the use of GPI and the selection of the dose for the prolonged bivalirudin infusion were not randomized, but rather left to the investigator's discretion and almost certainly influenced by the patient's clinical and procedural risk profile. In that regard, the results of this post-hoc analysis need to be interpreted with caution especially as it relates to the overall 30-day clinical outcomes that may be more directly related to patient and procedural factors rather than being indicative of treatment strategy performance.

Consistent with increasing adoption of the new $P2Y_{12}$ inhibitors in contemporary practice, approximately 50% of patients in EUROMAX were treated upstream with a loading dose of prasugrel or ticagrelor. However, our analysis found no influence of the choice of $P2Y_{12}$ inhibitor on the rates of AST. This observation is consistent with the pivotal trials for both agents that did not demonstrate significant reductions in the rates of AST compared with clopidogrel, but did indeed reduce the risk for subacute (>24 h and up to 30 days) ST (16,17). A plausible explanation for the inability of even the newer agents to prevent AST was provided by a recent study by Alexopoulos et al. (22), which demonstrated that onset of the expected platelet inhibition with prasugrel and ticagrelor can be delayed for up to 4 to 6 h in STEMI patients. With the vulnerable window for AST limited to the first few hours after pPCI, this delayed bioavailability of all the oral agents becomes important if bivalirudin is stopped immediately at the end of the procedure. The present analysis from EUROMAX suggests that this vulnerable period may be covered with a prolonged bivalirudin infusion at the PCI dose. This post-hoc observation needs prospective confirmation.

STUDY LIMITATIONS. The modeling used to determine the independent predictors of ST in this post-hoc analysis has several limitations. The rate of AST was extremely low at 0.6% (n = 14), therefore the ability to reliably discern predictors is limited. The model using Firth penalized maximum likelihood estimation may be a better-suited option when modeling rare events;

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however, the model is still not ideal. The list of variables in the regression model was selected post-hoc, and it is not certain that all variables that could be associated with AST were identified. Only 27% (n = 244) of bivalirudin patients received the BIV-PCI infusion dose post-procedure. Given this post-randomization analysis, the findings should be considered with caution and as hypothesis generating.

CONCLUSIONS

This analysis from EUROMAX confirms that the risk for AST is limited to the first few hours after pPCI and that neither the new oral $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) nor a low-dose (0.25 mg/kg/h) bivalirudin infusion are protective. However, prolonging the bivalirudin infusion at the full PCI dose for the first few hours after pPCI was not associated with a higher risk of AST while maintaining the lower bleeding rates, suggesting that this strategy could potentially further optimize outcomes in pPCI.

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